2015

Effects of levodopa on regional cerebral metabolism and blood flow

J. H. Ko
Northwell Health

R. P. Lerner
Northwell Health

D. Eidelberg
Hofstra Northwell School of Medicine

Published in final edited form as:
Mov Disord. 2015 January ; 30(1): 54–63. doi:10.1002/mds.26041.

Effects of Levodopa on Regional Cerebral Metabolism and Blood Flow

Ji Hyun Ko[1,2], **Renata P. Lerner**[1], and **David Eidelberg**[1,*]

[1]Center for Neurosciences, The Feinstein Institute for Medical Research, Manhasset, NY, USA

[2]Department of Human Anatomy and Cell Science, University of Manitoba, Winnipeg, MB, Canada (current address)

Abstract

Levodopa has been at the forefront of antiparkinsonian therapy for a half century. Recent advances in functional brain imaging have contributed substantially to the understanding of the effects of levodopa and other dopaminergic treatment on the activity of abnormal motor and cognitive brain circuits in Parkinson's disease patients. Progress has also been made in understanding the functional pathology of dyskinesias, a common side effect of levodopa treatment, at both regional and network levels. Here, we review these studies, focusing mainly on the new mechanistic insights provided by metabolic brain imaging and network analysis.

Keywords

levodopa; metabolism; blood flow; dopamine; positron emission tomography (PET)

Introduction

The dopamine precursor levodopa has been the most effective medication available for the treatment of Parkinson's disease (PD) in the past 50 years. Because PD is characterized by nigrostriatal dopamine deficiency, levodopa administration is expected to reverse the functional and neurochemical changes seen in the brains of PD patients. Brain imaging studies have largely supported this general mechanism with respect to the treatment of PD motor symptoms.[1–5] That said, the specific mechanisms underlying the cognitive and motor side effects of dopaminergic treatment remain poorly understood, despite the use of advanced research imaging tools.

Functional brain imaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance

*Correspondence to: David Eidelberg, MD, Center for Neurosciences, The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030., Phone: (516) 562-2498; Fax: (516) 562-1008; david1@nshs.edu.

Financial Disclosure/Conflict of Interest: Dr. Eidelberg serves on the scientific advisory board and has received honoraria from the Michael J. Fox Foundation for Parkinson's Research; is listed as coinventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same without financial gain; has received research support from the NIH (NINDS, NIDCD, NIAID) and the Dana Foundation; and has served as a consultant for Pfizer. All other authors declare no fiancial conflict of interest.

imaging (fMRI), have contributed greatly to the study of the effects of levodopa on neural activity on the regional and network levels. As a marker of synaptic activity, regional ^{18}F-fluorodeoxyglucose (FDG) uptake measured with PET has unique advantages in this regard. A number of FDG PET studies have examined the metabolic changes induced by levodopa treatment. Different analytical strategies have been employed to this end, such as mass univariate statistics and multivariate spatial covariance approaches, to examine isolated regions and whole brain networks, respectively.

The Abnormal PD State and the Metabolic Effects of Levodopa

When dopaminergic abnormalities were first described in PD,[6, 7] the contribution of other brain regions to the disease landscape was unknown. With the advent of FDG PET imaging in the 1980's, metabolic abnormalities became evident in the cerebral cortex of PD patients.[8] Subsequently, disease-related abnormalities in regional metabolic activity discerned with FDG PET were found to correlate with the loss of presynaptic nigrostriatal dopaminergic function measured with ^{18}F-fluorodopa (FDOPA) PET. Both metabolic activity and striatal FDOPA uptake correlated with independent motor ratings.[9] It has since been understood that in PD, dopamine deficiency results in brain-wide abnormalities, which are not restricted to the basal ganglia.[10–12] Thus, although dopaminergic imaging can be used for the direct assessment of presynaptic nigrostriatal terminals, metabolic imaging with FDG PET can be used to characterize circuit-level changes in cortico-striato-pallido-thalamo-cortical (CSPTC) loops and related pathways in the resting state. In particular, spatial covariance analysis of metabolic scans have been invaluable in identifying network abnormalities related to PD, and have resulted in the characterization of different patterns representing specific disease manifestations: akinesia-rigidity, tremor, and cognitive impairment.[13, 14] One of these patterns, the Parkinson's disease motor-related pattern (PDRP), is characterized by increased pallidothalamic and pontine metabolic activity, associated with covarying reductions in premotor, supplementary motor and parietal association regions (Fig. 1A). Expression values for this pattern consistently correlate with standardized motor disability ratings.[13, 15] Nonetheless, PDRP expression has recently been found to be abnormally elevated in the ipsilateral hemispheres of early stage patients with hemi-parkinsonism and in prodromal subjects with REM sleep behavior disorder (RBD).[16–18] Thus, the PDRP is sensitive to disease progression in the "premotor period" of PD, which antecedes the clinical onset of the actual movement disorder. The metabolic topography of the PDRP accords well with predictions based upon the classical "box and line" model of CSPTC motor circuitry.[19] In this vein, a close relationship was found between PDRP expression and spontaneous subthalamic nucleus (STN) neuronal firing rates recorded in PD patients undergoing DBS surgery.[20] Robust relationships also exist between PDRP subject scores and corresponding FDOPA PET measures of presynaptic nigrostriatal dopaminergic dysfunction obtained from the same individuals. A recent study of 106 PD subjects scanned with both FDG and FDOPA PET disclosed highly significant correlations between these measures (C. Eggers, personal communication). The magnitude of these correlations (r^2~0.20–0.30) was modest, however, relative to those between network expression and spontaneous STN cell activity (r^2~ 0.70). Thus, the human PD data suggest that PDRP expression in a given individual is associated more closely with factors regulating basal ganglia output rather than input.

Notably, a homologous metabolic covariance pattern closely resembling the human PDRP has recently been identified in FDG PET scans from macaques with parkinsonism induced by chronic systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration (Fig. 1B).[21] The development of an abnormal PDRP-like topography in this nonhuman primate model certainly relates the pattern to nigrostriatal dopamine loss. Given, though, that other neurotransmitter systems are also lesioned in this animal model,[22] one cannot conclude that the relationships observed between the PDRP network and dopamine are in any sense exclusive.

It is not known whether levodopa treatment modulates PDRP activity directly through dopaminergic projections to putaminal “front end” regions, or indirectly through functional modulation of pallidothalamic inhibitory outflow pathways by way of the STN,[23] or through a combination of the two effects. It is, however, readily apparent that the abnormal elevations in PDRP expression that typify the disorder are reduced by levodopa treatment (Fig. 1C).[1, 24, 25] Indeed, the degree of network suppression achieved by the drug in individual patients correlated with the improvement in motor ratings determined by an independent observer.[1, 25] This “network normalization” hypothesis is supported by fMRI data showing levodopa-mediated reductions in the overactive neural responses seen in PD subjects scanned in the baseline (off-medication) condition during the performance of a visuomotor task,[4] as well as partial restoration of neural functional connectivity during motor task performance.[5] Nonetheless, other fMRI studies have produced inconsistent findings, with increases as well as decreases in motor cortical activation in response to levodopa treatment.[26, 27] At least some of the differences between these studies can be attributed to reversal of the abnormal resting state increases in motor network activity seen in PD patients undergoing dopaminergic pharmacotherapy.[28] Indeed, by separately quantifying network expression at rest and during movement, this $H_2{}^{15}O$ PET study suggested that the dominant effect of levodopa was to lower the abnormal elevations in resting state motor network activity recorded at baseline in unmedicated PD subjects. Treatment-mediated changes in the motor activation response (measured, e.g., by the movement-rest difference in blood oxygen-level dependent (BOLD) fMRI signal) proved to be less robust than corresponding changes in resting state activity. Further research is needed to gain a better understanding of the mechanism of levodopa treatment at the systems level.

Levodopa Effects on Cognitive Function in Parkinson’s Disease

In addition to ameliorating motor manifestations of PD, levodopa impacts cognitive functioning in patients with this disorder. Spatial covariance analysis of FDG PET scans from PD patients has revealed a distinct metabolic topography unrelated to the PDRP, associated with performance on tests of memory and executive functioning in this population (Fig. 2A).[29] Expression values for this PD cognition-related metabolic pattern (PDCP) have been found to correlate consistently with performance on the California Verbal Learning test (CVLT), Trail Making Test B, and the Stroop Tests, as well as other tests involving executive functioning, such as the Symbol Digit Monitoring Test (SDMT) and the Hooper Visuospatial Orientation Test (HVOT)) (Fig. 2B).[15, 30] The PDCP topography is characterized by reductions in medial prefrontal, premotor and parietal activity, covarying

with relative increases in the cerebellum and brainstem. Increased PDCP expression has been associated with advancing cognitive impairment in PD populations, [30] although the progression rate for this network is generally slower than that for PDRP expression in the same subjects.[15, 17] In addition to displaying excellent test-retest reproducibility,[29] PDCP expression values appear to be relatively insensitive to potentially confounding placebo effects.[31] Computation of PDCP expression performed on a prospective individual case basis have revealed robust correlations between these values and measures of neuropsychological performance obtained at the time of imaging.[13, 31] Apart from providing further substantiation of PDCP expression as an imaging marker of executive dysfunction in PD, network analysis has demonstrated that the PDCP topography itself is highly replicable across populations (K. L. Leenders, personal communication). Needless to say, the validitiy of the PDCP is substantiated by its close topographic relationship with the pattern of cortical histopathological changes associated with cognitive impairment seen in PD postmortem specimens.[32]

In contrast to the uniform PDRP responses observed in PD subjects undergoing levodopa treatment, concurrent treatment-mediated changes in PDCP expression were substantially more varied when measured in the same individuals.[29] Interestingly, “cognitive responders” (i.e., subjects whose executive dysfunction improved with levodopa administration) exhibited concurrent treatment-mediated reductions in PDCP expression that were not seen in “cognitive non-responders” (i.e., subjects whose executive deficit did not improve during levodopa administration).[31] Of note, despite the differences in PDCP modulation that distinguished “cognitive responders” from “non-responders” to levodopa, significant treatment-mediated reductions in PDRP expression were present in both treatment subgroups. These results highlight the functional disparity between the motor and cognitive network changes that occur in individual patients during levodopa treatment.[3]

The data also suggest that the cognitive response to levodopa is influenced by baseline PDCP activity.[31, 33] That is, higher baseline network expression levels, which signify more advanced cognitive impairment in PD patients[15, 30] is associated with improved test performance during treatment. This supports the inverted U hypothesis of levodopa-learning (Fig. 2C).[34] PD subjects with greater baseline deficits (and higher baseline PDCP scores) also exhibited commensurately higher PDRP expression levels, signifying greater involvement of motor as well as cognitive disease networks. Such individuals may possess a greater degree of neurodegenerative change in the substantia nigra pars compacta, with dopaminergic cell loss extending beyond the ventral midbrain (which projects predominantly to the motor-related posterior putamen) into the dorsomedial midbrain (which projects to cognition-related caudate and anterior putamen). In support of this hypothesis, a recent dual-tracer study revealed a significant negative correlation between caudate DAT binding and PDCP expression.[33] Similarly, other studies have found correlations between degree of cognitive impairment and presynaptic dopaminergic ligand binding in both the caudate and putamen.[35, 36] Thus, patients with larger baseline deficits in caudate dopaminergic innervation are more likely to benefit cognitively from levodopa, with greater treatment-mediated PDCP modulation and concomitant improvement in executive functioning.[31] That said, data from a large cross-sectional PD sample suggest that PDCP expression continues to increase monotonically in PD subjects as cognitive impairment

progresses and evolves into actual dementia (Fig. 2D).[13, 30] It is likely that the substantial elevations observed in this context represent the development of inherent neurodegeneration involving cortical network regions,[32] rather than functional deafferentation effects. Cognitive dysfunction in such patients is unlikely to improve with dopaminergic pharmacotherapy despite the presence of high baseline PDCP levels.[14]

Relationship of Metabolic Activity to Dopaminergic Functioning

While many studies have examined either dopaminergic deficits or metabolic abnormalities in relation to the motor and cognitive manifestations of PD, only a few have directly examined the relationship between cerebral metabolism and nigrostriatal dopaminergic integrity.[9, 15, 17, 36] While both putaminal FDOPA uptake and PDRP expression correlate with parkinsonian bradykinesia and rigidity, gait dysfunction is likely associated with other neurotransmitters. Indeed, the risk of falling in PD has been linked to cholinergic dysfunction.[37] Moreover, both the motor and the non-motor manifestations of the disorder have been associated with deficits in more than one neurotransmitter system.[38, 39]

Some insight into the relationships between nigrostriatal dopaminergic integrity, metabolic network expression, and the clinical manifestations of PD has been achieved through dual tracer radionuclide imaging. A recent large scale dual tracer PET study (C. Eggers, personal communication) rigorously assessed the relationship between loss of nigrostriatal dopaminergic terminals (quantified with FDOPA PET) and PDRP/PDCP expression values (quantified with FDG PET) in individual PD subjects. As in other studies, modest correlations were discerned between these measures. Specifically, PDCP expression correlated with caudate FDOPA uptake. By contrast, after adjusting for individual differences in PDCP expression, PDRP values were found to correlate with FDOPA uptake in the posterior putamen.[33] Still, the magnitude of these correlations was weaker than the more robust correlations that were previously demonstrated between PDRP activity and basal ganglia output as measured by spontaneous STN firing rates in awake, alert PD patients.[20] These findings suggest that although presynaptic dopamine loss in PD is associated with a characteristic set of disease-related metabolic abnormalities at the regional and systemic levels, these changes can hardly be viewed as interchangeable. Indeed, the network-level abnormalities seen in PD cannot be readily ascribed to functional/anatomical changes involving a single neurotransmitter system.

Blood Flow-Cerebral Metabolism Dissociation Induced by Levodopa

Quantitative measurements of metabolic network activity have provided important systems level information concerning the action of levodopa and other therapeutic interventions resting state cerebral function in PD subjects. Indeed, as observed with levodopa, stereotaxic surgical procedures, such as high frequency STN deep brain stimulation (DBS),[1, 40] lesioning (subthalamotomy),[41] and subthalamic gene therapy with an adeno-associated virus (AAV) borne glutamic acid decarboxylase (GAD) gene.[42] have been found to modulate PDRP but not PDCP activity in the course of treatment.[14] As also seen with levodopa, clinical outcomes following treatment correlated with the degree to which abnormal baseline PDRP elevations were suppressed (normalized) by the intervention.[1, 14] Unexpectedly,

though, when the effects of levodopa on PDRP expression were compared in concurrently acquired scans of cerebral metabolism (FDG PET) and blood flow ($H_2{}^{15}O$ PET) from PD subjects, a marked dissociation between the two network response measures was observed at the individual patient level.[43] In the unmedicated baseline state (12 hours off levodopa), a close correlation was present between PDRP expression values computed in scans of cerebral metabolic rate (CMR) glucose and cerebral blood flow (CBF) from the same individuals.[44] Indeed, analogous correlations have been observed between network values computed in FDG PET and scans of cerebral perfusion obtained with $H_2{}^{15}O$ PET or, non-invasively, using arterial spin labeling MRI methods.[45] While CMR and CBF network measures are highly intercorrelated in PD patients scanned off medication, Hirano and colleagues found that levodopa treatment resulted in a dissociation between these effects (Fig. 3A). Whereas effective PD treatment with STN DBS was found to reduce abnormally elevated metabolic network activity in CMR as well as CBF scans,[43] levodopa titrated to achieve comparable clinical benefit resulted in consistent CBF increases, despite the presence of concurrent reductions in network activity in CMR scans acquired in the same subjects (Fig. 3B). Interestingly, PD patients experiencing levodopa-induced dyskinesias (LIDs) were found to have substantially higher on-state CBF in PDRP regions, than their non-dyskinetic counterparts.[43] By contrast, however, levodopa-mediated reductions in CMR in these areas were of similar magnitude in LID and non-LID subjects. These divergent effects suggest that levodopa exerts distinct hemodynamic effects in network regions, apart from the correction in abnormally elevated synaptic activity that is concurrently observed in the same brain areas.

The mechanism of levodopa-mediated flow-metabolism dissociation was investigated in an autoradiographic study of the unilateral 6-hydroxydopamine (6-OHDA) lesioned rat.[46] The results closely paralleled the human imaging findings: rats acutely and chronically treated with levodopa exhibited uncoupling of CBF and CMR in the striatum and globus pallidus (GP) and in the primary motor cortex. With chronic treatment, the rats also exhibited increase in blood brain barrier (BBB) permeability involving the striatum and substantia nigra, as well as an increase in on-state CBF in these regions. In a recent dual tracer (FDG and $H_2{}^{15}O$) microPET study conducted in the awake unilateral 6-OHDA rat model,[47] there was evidence (Fig. 4A) of a significant CBF/CMR dissociation in the ipsilateral striatum after treatment with a single levodopa injection. Of note, this treatment-mediated increase in local CBF was observed while the animals were under anesthesia (Fig. 4B). It is therefore likely that the observed changes are unrelated to concurrent motor manifestations.[46, 47] Moreover, the autoradiography results suggest that the increases in local CBF that accompany the induction of LID may be associated with a concurrent BBB breach in the same brain regions.[46] Studies are in progress using the rat model to examine the specific changes in CBF/CMR coupling that take place following chronic levodopa treatment and the induction of dyskinesias (see below). Parallel studies are being conducted to assess the relationship between levodopa-mediated flow-metabolism dissociation, BBB permeability, and the occurrence of LID in human PD subjects.

Vascular Changes with Chronic Levodopa Treatment: Association with LID

The concept of neurovascular coupling is associated with the phenomenon of functional hyperemia, which relates the brain CBF regulation to synaptic activity.[48] The cerebral vasculature is known to be coordinately controlled by neurovascular mechanisms, which ensure that blood delivery matches neuronal energy needs such that under most physiological conditions, increases in synaptic activity result in parallel increases in local CBF. Nonetheless, uncoupling has been reported in different conditions, in health, disease or after pharmacological treatment,[43, 49, 50] and molecular studies provide potential mechanisms for this phenomenon.[51–53] An early study conducted in the unilateral 6-OHDA rat model to examine the cellular effects of chronic levodopa treatment[52] revealed endothelial proliferation and likely angiogenesis involving the striatum and its output structures. Indeed, these changes were highlighted by increased staining for nestin (a model marker of immature endothelial cells) as well as decreased staining of endothelial barrier antigen on the blood vessel wall (a marker of vasculature integrity). A subsequent study utilizing the same animal model[51] found that chronic levodopa treatment induced expression of vascular endothelial growth factor (VEGF) in the basal ganglia in a dose dependent fashion. In this model, VEGF was expressed predominantly in astrocytes and astrocytic processes near blood vessels. In parallel, the authors used the UK Brain Bank to examine postmortem tissue from chronically levodopa treated PD patients. They found increased nestin staining and VEGF mRNA expression in the striatum of these specimens.

What could be the significance then of this levodopa-mediated CBF-CMR uncoupling and of the vascular changes observed in the brain of animal models and postmortem tissue of PD patients? Previously, levodopa-mediated flow-metabolism dissociation was demonstrated in chronically treated PD patients. While the phenomenon was identified as a consistent response to levodopa administration in PD subjects without LID, flow-metabolism dissociation was particularly pronounced in the small number of individuals with this complication of treatment.[43] Indeed, in that study, the increase in CBF observed with levodopa administration correlated with duration of treatment. Moreover, in the rat model, endothelial proliferation, likely reflecting underlying angiogenesis, was featured specifically in animals with discernible dyskinesias.[52] In a subsequent study,[51] administration of a VEGF signaling inhibitor blocked the appearance of markers of BBB permeability (albumin extravasation) and angiogenic response (nestin and VEGF expression) that were seen in vehicle-treated rats after chronic levodopa treatment. Furthermore, VEGF inhibition significantly attenuated the expression of dyskinesias in LID animals.[51]

LID is currently thought to relate to pre- and post-synaptic changes that result in dopaminergic imbalance.[54] Indeed, postsynaptic changes likely play an import role in LID development. This point is illustrated in a recent case report[55] describing a patient who developed LID after chronic treatment of a non-progressive post-traumatic lesion. That said, a recent report[56] suggests that the development of LID relates to the degree of dopaminergic denervation present at baseline in the putamen. This observation, if confirmed, strongly implicates presynaptic mechanisms in the development of LID. Independently, in both PD patients and rodent models, dyskinesias have been associated with larger increases in striatal extracellular DA levels after levodopa administration.[57, 58] Entry of levodopa into the brain

is regulated by endothelial cells at the blood-brain barrier. Moreover, vascular smooth muscle contraction is regulated to a substantial degree by dopamine D1 receptors.[59] At antiparkinsonian treatment doses, dopamine binding to vasculature receptors is likely to result in vasodilation and local blood flow increases.[60] This increase in local CBF may not, however, be beneficial in the long term. As noted above, chronic levodopa administration been shown in the rat model to induce endothelial proliferation and microvasculature alterations in dyskinetic animals.

Thus, it is tempting to speculate that chronic levodopa treatment leads to the development of microvascular changes such as angiogenesis, which under specific circumstances, can enhance the transport of the drug across the BBB. Indeed, the autoradiographic data suggest that enhanced BBB permeability, as well as concurrent increases in local CBF, are dopamine dependent phenomena that are not present in the off-state. That, in fact, may explain earlier observations of intact BBB permeability in parkinsonian non-human primates scanned in the absence of medication.[61] According to our model, newly formed vessels may be supersensitive to dopamine, and the resulting CBF increase following levodopa administration, leads to an increase in perfusion pressure, and a treatment state-dependent breach of the BBB in brain regions, characterized specifically by increased local dopa decarboxylase (DDC) expression and comparatively large numbers of vascular dopamine receptors. Recent data from PD subjects receiving levodopa infusions during combined FDG and $H_2{}^{15}O$ PET scanning confirmed that dopamine-mediated hemodynamic responses were elevated in LID vs. non-LID subjects, and that capillary reserve in areas of levodopa-mediated flow-metabolism dissociation was also increased in the former group. These findings are consistent with a recent fMRI study in which putamen activity was elevated in LID patients attempting to suppress involuntary movements relative to their non-LID counterparts.[62] More research is needed to determine whether the degree of flow-metabolism dissociation seen in PD patients is predictive of the subsequent development of LID in these individuals.

Future Directions

Advances in imaging technology, computational methods, and data analysis have led to a better understanding of how levodopa acts to improve quality of life for PD patients. The use of objective, voxel-based image analysis tools to assess nigrostriatal dopaminergic loss in PD subjects, in conjunction with advanced mapping approaches to evaluate the effects of these and related neurotransmitter changes on brain function, have provided a rigorous means of quantifying disease progression and treatment effects at the systems level. Recent work has shown the utility of this multi-modal approach in characterizing the circuit changes that underlie cognitive and motor disease manifestations. In particular, the results of network analysis have shed light on the mechanism by which levodopa affects cognitive functioning in PD patients, as well as the distinct neurovascular changes that underlie the occurrence of LID in these individuals. This unique information may help in the development of new treatment strategies directed at these major clinical challenges.

Acknowledgments

Funding Source: This work was supported in part by the National Institute of Neurological Disorders and Stroke Morris K. Udall Center of Excellence for Parkinson's Disease Research at The Feinstein Institute for Medical Research (P50 NS071675 to D.E.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health. The sponsor did not play a role in study design, collection, analysis and interpretation of data, writing of the report or in the decision to submit the paper for publication.

References

1. Asanuma K, Tang C, Ma Y, et al. Network modulation in the treatment of Parkinson's disease. Brain. 2006; 129(Pt 10):2667–2678. [PubMed: 16844713]
2. Herz DM, Siebner HR, Hulme OJ, Florin E, Christensen MS, Timmermann L. Levodopa reinstates connectivity from prefrontal to premotor cortex during externally paced movement in Parkinson's disease. Neuroimage. 2014; 90:15–23. [PubMed: 24269570]
3. Jubault T, Monetta L, Strafella AP, Lafontaine AL, Monchi O. L-dopa medication in Parkinson's disease restores activity in the motor cortico-striatal loop but does not modify the cognitive network. PLoS One. 2009; 4(7):e6154. [PubMed: 19584921]
4. Ng B, Palmer S, Abugharbieh R, McKeown MJ. Focusing effects of L-dopa in Parkinson's disease. Hum Brain Mapp. 2010; 31(1):88–97. [PubMed: 19585587]
5. Palmer SJ, Eigenraam L, Hoque T, McCaig RG, Troiano A, McKeown MJ. Levodopa-sensitive, dynamic changes in effective connectivity during simultaneous movements in Parkinson's disease. Neuroscience. 2009; 158(2):693–704. [PubMed: 18722512]
6. Hornykiewicz O. Dopamine (3-hydroxytyramine) in the central nervous system and its relation to the Parkinson syndrome in man. Deutsche medizinische Wochenschrift. 1962; 87:1807–1810. [PubMed: 14448985]
7. O'Reilly S, Loncin M, Cooksey B. Dopamine and basal ganglia disorders. Neurology. 1965; 15(11): 980–984. [PubMed: 5892413]
8. Kuhl DE, Metter EJ, Riege WH. Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [18F]fluorodeoxyglucose method. Ann Neurol. 1984; 15(5):419–424. [PubMed: 6610384]
9. Eidelberg D, Moeller JR, Dhawan V, et al. The metabolic anatomy of Parkinson's disease: complementary [18F]fluorodeoxyglucose and [18F]fluorodopa positron emission tomographic studies. Mov Disord. 1990; 5(3):203–213. [PubMed: 2117706]
10. Herman T, Giladi N, Hausdorff JM. Neuroimaging as a window into gait disturbances and freezing of gait in patients with Parkinson's disease. Curr Neurol Neurosci Rep. 2013; 13(12):411. [PubMed: 24136458]
11. Herz DM, Florin E, Christensen MS, et al. Dopamine Replacement Modulates Oscillatory Coupling Between Premotor and Motor Cortical Areas in Parkinson's Disease. Cereb Cortex. 2013 Epub ahead of print.
12. Sabatini U, Boulanouar K, Fabre N, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain. 2000; 123 (Pt 2):394–403. [PubMed: 10648446]
13. Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. Trends Neurosci. 2009; 32(10):548–557. [PubMed: 19765835]
14. Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: concepts and applications. Ann of Neurol. 2012; 72(5):635–647. [PubMed: 22941893]
15. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson's disease. Brain. 2007; 130(Pt 7):1834–1846. [PubMed: 17470495]
16. Holtbernd F, Gagnon JF, Postuma RB, et al. Abnormal metabolic network activity in REM sleep behavior disorder. Neurology. 2014; 82(7):620–627. [PubMed: 24453082]
17. Tang CC, Poston KL, Dhawan V, Eidelberg D. Abnormalities in metabolic network activity precede the onset of motor symptoms in Parkinson's disease. J Neurosci. 2010; 30(3):1049–1056. [PubMed: 20089913]

18. Wu P, Wang J, Peng S, et al. Metabolic brain network in the Chinese patients with Parkinson's disease based on 18F-FDG PET imaging. Parkinsonism Relat Disord. 2013; 19(6):622–627. [PubMed: 23529021]
19. DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol. 2007; 64(1):20–24. [PubMed: 17210805]
20. Lin TP, Carbon M, Tang C, et al. Metabolic correlates of subthalamic nucleus activity in Parkinson's disease. Brain. 2008; 131(Pt 5):1373–1380. [PubMed: 18400841]
21. Ma Y, Peng S, Spetsieris PG, Sossi V, Eidelberg D, Doudet DJ. Abnormal metabolic brain networks in a nonhuman primate model of parkinsonism. J Cereb Blood Flow Metab. 2012; 32(4): 633–642. [PubMed: 22126913]
22. Pifl C, Schingnitz G, Hornykiewicz O. Effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on the regional distribution of brain monoamines in the rhesus monkey. Neuroscience. 1991; 44(3): 591–605. [PubMed: 1754053]
23. Levy R, Dostrovsky JO, Lang AE, Sime E, Hutchison WD, Lozano AM. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with Parkinson's disease. J Neurophysiol. 2001; 86(1):249–260. [PubMed: 11431506]
24. Berding G, Odin P, Brooks DJ, et al. Resting regional cerebral glucose metabolism in advanced Parkinson's disease studied in the off and on conditions with [(18)F]FDG-PET. Mov Disord. 2001; 16(6):1014–1022. [PubMed: 11748732]
25. Feigin A, Fukuda M, Dhawan V, et al. Metabolic correlates of levodopa response in Parkinson's disease. Neurology. 2001; 57(11):2083–2088. [PubMed: 11739830]
26. Buhmann C, Glauche V, Sturenburg HJ, Oechsner M, Weiller C, Buchel C. Pharmacologically modulated fMRI--cortical responsiveness to levodopa in drug-naive hemiparkinsonian patients. Brain. 2003; 126(Pt 2):451–461. [PubMed: 12538411]
27. Haslinger B, Erhard P, Kampfe N, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain. 2001; 124(Pt 3):558–570. [PubMed: 11222456]
28. Ko JH, Mure H, Tang CC, et al. Parkinson's Disease: Increased Motor Network Activity in the Absence of Movement. J Neurosci. 2013; 33(10):4540–4549. [PubMed: 23467370]
29. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. Neuroimage. 2007; 34(2):714–723. [PubMed: 17113310]
30. Huang C, Mattis P, Perrine K, Brown N, Dhawan V, Eidelberg D. Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology. 2008; 70(16 Pt 2): 1470–1477. [PubMed: 18367705]
31. Mattis PJ, Tang CC, Ma Y, Dhawan V, Eidelberg D. Network correlates of the cognitive response to levodopa in Parkinson disease. Neurology. 2011; 77(9):858–865. [PubMed: 21849641]
32. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24(2):197–211. [PubMed: 12498954]
33. Niethammer M, Tang CC, Ma Y, et al. Parkinson's disease cognitive network correlates with caudate dopamine. Neuroimage. 2013; 78:204–209. [PubMed: 23578575]
34. Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry. 2011; 69(12):e113–125. [PubMed: 21531388]
35. Cheesman AL, Barker RA, Lewis SJ, Robbins TW, Owen AM, Brooks DJ. Lateralisation of striatal function: evidence from 18F-dopa PET in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005; 76(9):1204–1210. [PubMed: 16107352]
36. Polito C, Berti V, Ramat S, et al. Interaction of caudate dopamine depletion and brain metabolic changes with cognitive dysfunction in early Parkinson's disease. Neurobiol Aging. 2012; 33(1): 206, e229–239. [PubMed: 20961661]
37. Bohnen NI, Muller ML, Koeppe RA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. Neurology. 2009; 73(20):1670–1676. [PubMed: 19917989]

38. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol. 2003; 60(12):1745–1748. [PubMed: 14676050]
39. Ray NJ, Strafella AP. The neurobiology and neural circuitry of cognitive changes in Parkinson's disease revealed by functional neuroimaging. Mov Disord. 2012; 27(12):1484–1492. [PubMed: 23038645]
40. Wang J, Ma Y, Huang Z, Sun B, Guan Y, Zuo C. Modulation of metabolic brain function by bilateral subthalamic nucleus stimulation in the treatment of Parkinson's disease. J Neurol. 2010; 257(1):72–78. [PubMed: 19662326]
41. Trost M, Su S, Su P, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. Neuroimage. 2006; 31(1):301–307. [PubMed: 16466936]
42. Feigin A, Kaplitt MG, Tang C, et al. Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease. Proc Natl Acad Sci U S A. 2007; 104(49):19559–19564. [PubMed: 18042721]
43. Hirano S, Asanuma K, Ma Y, et al. Dissociation of metabolic and neurovascular responses to levodopa in the treatment of Parkinson's disease. J Neurosci. 2008; 28(16):4201–4209. [PubMed: 18417699]
44. Ma Y, Tang C, Spetsieris PG, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. J Cereb Blood Flow Metab. 2007; 27(3):597–605. [PubMed: 16804550]
45. Ma Y, Huang C, Dyke J, et al. Parkinson's disease spatial covariance pattern: Non-invasive quantification with perfusion MRI. J Cereb Blood Flow Metab. 2010; 30(3):505–509. [PubMed: 20051975]
46. Ohlin KE, Sebastianutto I, Adkins CE, Lundblad C, Lockman PR, Cenci MA. Impact of L-DOPA treatment on regional cerebral blood flow and metabolism in the basal ganglia in a rat model of Parkinson's disease. Neuroimage. 2012; 61(1):228–239. [PubMed: 22406356]
47. Lerner RP, Bimpisidis Z, Dewey S, et al. Dissociation between metabolic and neurovascular responses to levodopa treatment in a rat model of Parkinson's disease [abstract]. Mov Disord. 2014; 29(Suppl 1):216.
48. Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. Nat Neurosci. 2007; 10(11):1369–1376. [PubMed: 17965657]
49. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008; 57(2):178–201. [PubMed: 18215617]
50. Paulson OB, Hasselbalch SG, Rostrup E, Knudsen GM, Pelligrino D. Cerebral blood flow response to functional activation. J Cereb Blood Flow Metab. 2010; 30(1):2–14. [PubMed: 19738630]
51. Ohlin KE, Francardo V, Lindgren HS, et al. Vascular endothelial growth factor is upregulated by L-dopa in the parkinsonian brain: implications for the development of dyskinesia. Brain. 2011; 134(Pt 8):2339–2357. [PubMed: 21771855]
52. Westin JE, Lindgren HS, Gardi J, et al. Endothelial proliferation and increased blood-brain barrier permeability in the basal ganglia in a rat model of 3,4-dihydroxyphenyl-L-alanine-induced dyskinesia. J Neurosci. 2006; 26(37):9448–9461. [PubMed: 16971529]
53. Lindgren HS, Ohlin KE, Cenci MA. Differential involvement of D1 and D2 dopamine receptors in L-DOPA-induced angiogenic activity in a rat model of Parkinson's disease. Neuropsychopharmacology. 2009; 34(12):2477–2488. [PubMed: 19606087]
54. Cenci MA, Lundblad M. Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia. J Neurochem. 2006; 99(2):381–392. [PubMed: 16942598]
55. Pita Lobo P, Coelho M, Mestre TA, Rosa MM, Ferreira JJ. Wearing-off phenomena and levodopa-induced dyskinesias in posttraumatic hemiparkinsonism. Mov Disord. 2013; 28(9):1212–1214. [PubMed: 23861327]
56. Hong JY, Oh JS, Lee I, et al. Presynaptic dopamine depletion predicts levodopa-induced dyskinesia in de novo Parkinson disease. Neurology. 2014; 82(18):1597–1604. [PubMed: 24719485]
57. Lindgren HS, Andersson DR, Lagerkvist S, Nissbrandt H, Cenci MA. L-DOPA-induced dopamine efflux in the striatum and the substantia nigra in a rat model of Parkinson's disease: temporal and

quantitative relationship to the expression of dyskinesia. J Neurochem. 2010; 112(6):1465–1476. [PubMed: 20050978]

58. de la Fuente-Fernandez R, Sossi V, Huang Z, et al. Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain. 2004; 127(Pt 12):2747–2754. [PubMed: 15329355]
59. Krimer LS, Muly EC 3rd, Williams GV, Goldman-Rakic PS. Dopaminergic regulation of cerebral cortical microcirculation. Nat Neurosci. 1998; 1(4):286–289. [PubMed: 10195161]
60. Iadecola C. Neurogenic control of the cerebral microcirculation: is dopamine minding the store? Nat Neurosci. 1998; 1(4):263–265. [PubMed: 10195155]
61. Astradsson A, Jenkins BG, Choi JK, et al. The blood-brain barrier is intact after levodopa-induced dyskinesias in parkinsonian primates--evidence from in vivo neuroimaging studies. Neurobiol Dis. 2009; 35(3):348–351. [PubMed: 19501164]
62. Herz DM, Haagensen BN, Christensen MS, et al. The acute brain response to levodopa heralds dyskinesias in Parkinson disease. Ann Neurol. 2014; 75(6):829–836. [PubMed: 24889498]
63. Pourfar M, Tang C, Lin T, Dhawan V, Kaplitt MG, Eidelberg D. Assessing the microlesion effect of subthalamic deep brain stimulation surgery with FDG PET. J Neurosurg. 2009; 110(6):1278–1282. [PubMed: 19301972]
64. Mure H, Hirano S, Tang CC, et al. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. Neuroimage. 2011; 54(2):1244–1253. [PubMed: 20851193]
65. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991; 59(1):12–19. [PubMed: 2002127]
66. Maassen GH. The standard error in the Jacobson and Truax Reliable Change Index: the classical approach to the assessment of reliable change. J Int Neuropsychol Soc. 2004; 10(6):888–893. [PubMed: 15637779]

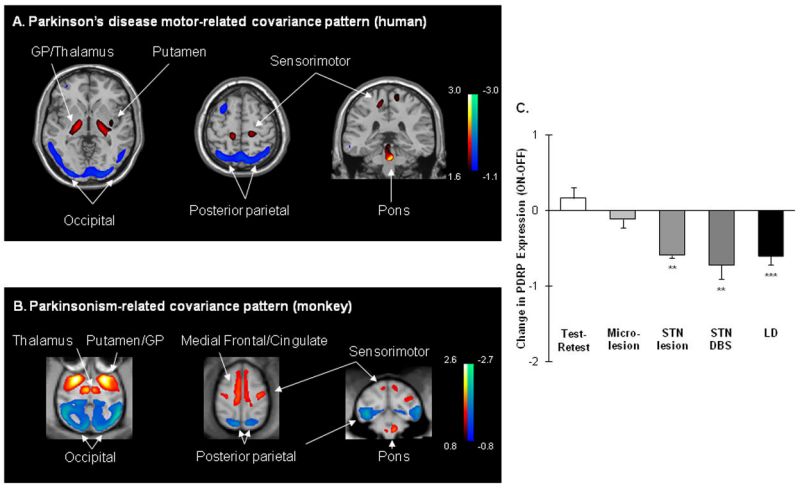

Figure 1.

Overlays illustrating regional homologies between the abnormal metabolic covariance patterns identified in human patients with idiopathic Parkinson's disease (PD) and monkeys with experimental parkinsonism induced by systemic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure. **(A)** The abnormal PD motor-related spatial covariance pattern (PDRP) identified consistently in multiple independent patient cohorts.[13, 14] **(B)** Parkinsonism-related spatial covariance pattern (PRP) identified by the analysis of FDG PET scans acquired in MPTP-lesioned and normal macaque monkeys. The PRP spatial topography was similar to that of the PDRP; similar metabolic changes were observed in homologous brain regions comprising the two covariance patterns. [Both spatial covariance patterns were displayed on standard MRI brain templates. Voxels with positive loadings (metabolic increases) are color-coded from red to yellow; those with negative loadings (relative metabolic reductions) are color-coded from blue to green.] **(C)** Treatment-mediated changes in PDRP expression (mean±SE) following stereotactic surgical interventions (*shaded bars*) targeting the subthalamic nucleus (STN): microlesion (n=6),[63] subthalamotomy (n=6),[41] and deep brain stimulation (DBS) (n=18).[64] Changes in network expression during levodopa (LD) administration (n=18)[31] (*solid bar*), as well as the test-retest variability of this measure (n=14)[1] (*open bar*) are depicted for comparison. Significant PDRP modulation was evident following subthalamotomy, STN DBS, and levodopa treatment but not microlesion. [**p<0.01, ***p<0.001 for the comparison of changes in PDRP expression with each intervention with those observed during test-retest evaluation, RMANOVA.] [**A, B:** Adapted from J Cereb Blood Flow Metab, Y. Ma et al. Abnormal metabolic brain networks in a nonhuman primate model of parkinsonism, 2012; 32(4): 633–642.[21] **C:** Adapted from Ann Neurol, M. Niethammer and D. Eidelberg. Metabolic brain networks in translational neurology: concepts and applications, 72(5): 635–647, Copyright (2012),[14] with permission from John Wiley and Sons.]

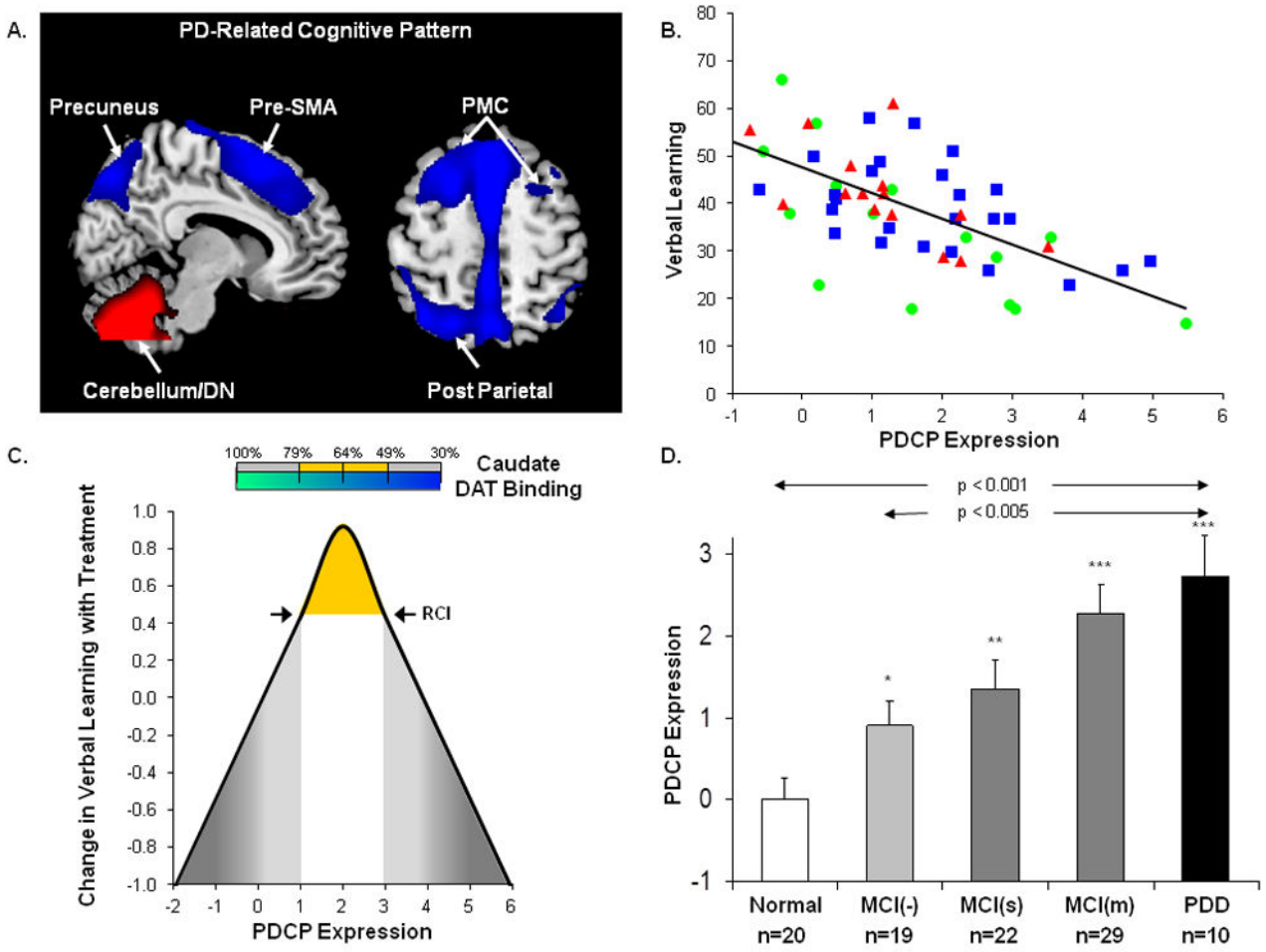

Figure 2.

(A) Parkinson's disease cognition-related covariance pattern (PDCP). This covariance pattern is characterized by reduced metabolic activity in the dorsal premotor cortex, rostral supplementary motor area (preSMA), precuneus, and posterior parietal regions, associated with relatively increased activity in the cerebellum.[15] [In the representative slices, relative metabolic increases are displayed in red; relative metabolic decreases are displayed in blue. Slices were overlaid on a standard MRI brain template.] **(B)** PDCP expression correlates with performance on neuropsychological tests of memory and executive functioning in non-demented PD patients. For the California Verbal Learning Test: Sum 1 to 5 (CVLT sum), this correlation was significant for the entire cohort (n=56; r=−0.67, p<0.001), as well as for the original group used for pattern derivation (*circles*; n=15: r=−0.71, p=0.003) and in two prospective validation groups (*squares*; n=25: r=−0.53, p=0.007; *triangles*; n=16: r=−0.80, p<0.001).[15] **(C)** Hypothetical relationship between levodopa-mediated changes in cognitive performance, baseline PDCP expression, and caudate dopamine transporter (DAT) binding. Based upon published data,[31, 33] we propose that an inverted U-shaped relationship exists between the changes in cognitive functioning observed during levodopa treatment (*y*-axis) and baseline measurements of caudate dopaminergic input (*horizontal bar*) and PDCP metabolic network activity (*x*-axis). The numbers at the top of the horizontal bar represent

the caudate DAT binding values that correspond to PDCP scores of 1.0, 2.0, and 3.0, respectively. These estimates were based upon the best fitting linear relationship of the two measures (mean caudate DAT binding = 0.94–0.15*PDCP score). The area under the curve associated with treatment-mediated cognitive benefit (*yellow*) was defined by an increase in individual subject test performance exceeding the independently determined Reliable Change Index (RCI)[65, 66] on the psychometric outcome measure. For verbal learning performance, the RCI cutoff (*arrows*) was determined to be 0.44, which is hypothesized to correspond to PDCP scores between +1.0 and +3.0.[31] No cognitive benefit during treatment is expected for PDCP values on either side of this interval (*gray*). **(D)** Bar graph of PDCP expression (mean±SE) in normal subjects, PD subjects without mild cognitive impairment (MCI(−)), with single and multiple domain mild cognitive impairment (MCI(s) and MCI(m)), and with Parkinson's disease dementia (PDD). There was a significant difference in PDCP expression across the patient and control groups ($F(4,70)=8.87$, $p<0.001$; one-way ANOVA), and among the PD groups ($F(3,56)=4.84$; $p<0.005$), with higher expression in the PDD and MCI(m) cohorts compared to the MCI(−) cohort ($p<0.03$; Tukey-Kramer HSD). [For each PD group, PDCP expression was separately compared to healthy control values using Student's *t*-tests. The asterisks denote significant increases in network activity relative to controls (*$p<0.05$, **$p<0.005$, ***$p<0.0001$) in all PD categories including MCI(−).] [**A, B, D:** Reprinted from Trends Neurosci, D. Eidelberg. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach, 32(10): 548–557, Copyright (2009),[13] with permission from Elsevier. **C:** Reprinted from Neuroimage, M. Niethammer et al. Parkinson's disease cognitive network correlates with caudate dopamine, 78: 204–209, Copyright (2013),[33] with permission from Elsevier.]

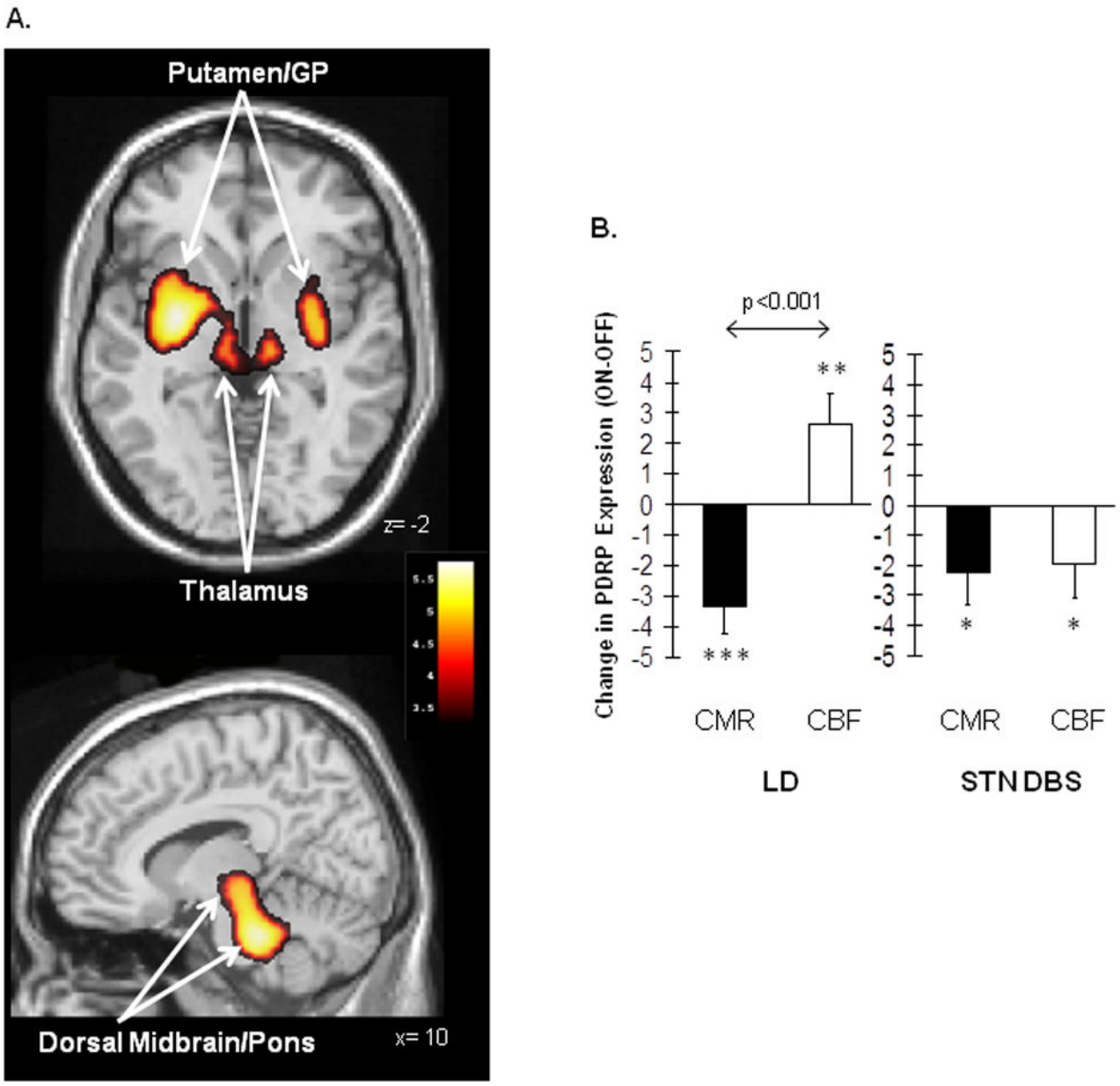

Figure 3.

(A) Results of voxel-based searches for brain regions with significant flow-metabolism dissociation in response to acute levodopa treatment.[43] *Top:* Treatment-mediated dissociation of regional glucose metabolism and cerebral blood flow is present bilaterally in the posterior-lateral putamen and adjacent globus pallidus (GP), and in the ventral thalamus. *Bottom*: Significant dissociation effects with levodopa are also present in the dorsal pons and midbrain. [Metabolic increases are displayed using a red-yellow scale. Both displays were superimposed on a single-subject MRI brain template and thresholded at T=3.28, p=0.001, extent threshold >50 voxels (peak voxel, uncorrected).] **(B)** Bar graph illustrating treatment-mediated changes (mean±SE) in the expression of the Parkinson's disease motor-related covariance pattern (PDRP) measured in scans of cerebral metabolic rate for glucose (CMR;

filled bars) and cerebral blood flow (CBF; *open bars*) acquired in the same group of PD subjects.[43] At the network level, a significant dissociation between the CMR and CBF treatment responses ($p<0.001$) is present with levodopa (LD) (*left*), but not with subthalamic nucleus deep brain stimulation (STN DBS) (*right*). [***$p<0.005$; **$p<0.01$; *$p<0.05$, post-hoc Bonferonni comparisons of ON vs. OFF values for each treatment group.] [**A, B:** Adapted from J Neurosci, S. Hirano et al. Dissociation of metabolic and neurovascular responses to levodopa in the treatment of Parkinson's disease, 28(16): 4201–4209, Copyright (2008),[43] with permission from Society for Neuroscience.]

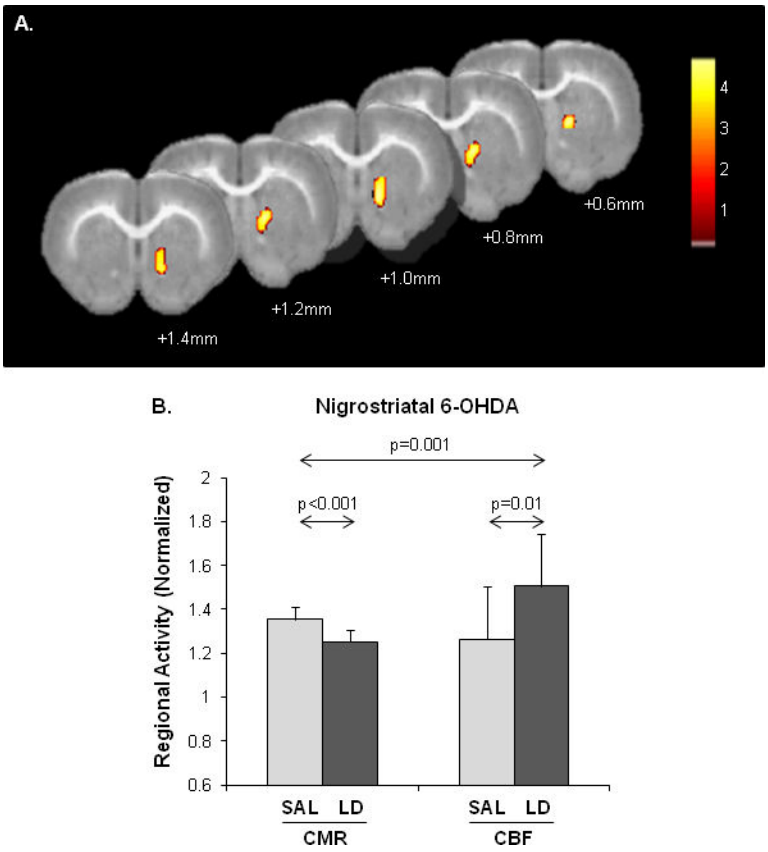

Figure 4.

(A) Area of flow-metabolism dissociation in the striatum of the 6-OHDA lesioned rat.[47] In this unilateral model of nigrostriatal dopaminergic denervation, flow-metabolism dissociation was present on the lesioned side following acute levodopa administration. **(B)** Flow-metabolism dissociation in this brain region reflected local CMR reductions taking place concurrently with increased CBF during levodopa (LD) treatment. Analogous changes were not present in the same area following saline (SAL) administration.